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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,712	05/15/2006	Christian Hesslinger	27319U	6309

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	**PAPER NUMBER**
4173	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,712	HESSLINGER ET AL.	
	Examiner	Art Unit	
	Marcos L. Sznaidman	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-18 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-18 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-7, 10-18 and 23 are currently pending and are the subject of this office action. Claims 8-9 and 19-22 have been cancelled. Claims 1-7, 10-18 and 23 are presently under examination. This is the First Office Action on the Merits of the Claims.

Priority

The present application claims priority to International Application No. PCT/EP04/52725 filed 10/29/2004 and to foreign application No. EP20030024844 filed 10/31/2003.

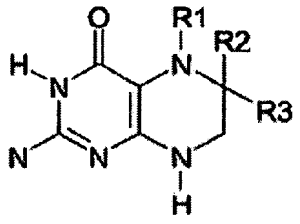
Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10-18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7, 10-18 and 23 recite a method for treating a respiratory disease, or a commercial product, or a preparation, or a pharmaceutical composition, or a trade package, comprising BH4 or a derivative thereof, or BH4 or a derivative thereof and arginine or a derivative thereof. However the specification discloses a general structure as shown in page 3 of the specification for the term BH4 (tetrahydrobioprotein):



with a limited number of substituents for R1, R2 and R3. It also discloses only 6 specific BH4 derivatives (see structures on pages 3 and 4 of the specification), which are contained within the previous formula. So there is no proof that the applicant was in possession of all the derivatives of BH4, except for those contained within the general structure shown above. The specification also discloses that the term "arginine or derivatives thereof" means arginine, preferably L-arginine, precursors of arginine, pharmaceutically acceptable derivatives of arginine, etc (bottom of page 9 of the specification). This definition does not show that the applicant was in possession of the broader claim: derivatives of arginine, except for L-arginine itself.

Claims 1-7 and 11-15 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a respiratory disease, does not reasonably provide enablement for preventing a respiratory disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping

that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

Claims 1-7 and 11-15 recite a method for preventing and/or treating a respiratory disease comprising administering a therapeutically effective amount of BH4 or a derivative thereof (or BH4 or a derivative thereof and arginine or a derivative thereof) to a patient in need thereof.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and prevention of a respiratory disease is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable). Although prior art offers evidence for the treatment of respiratory, there is no evidence that any repiratory

disease could be prevented by any treatment. As illustrative of the state of the art, the examiner cites Becker et. al. (Current opinion in pulmonary medicine (2002), 8:16-24).

Becker at. al. mention that although many guidelines exist for the treatment of asthma, there are almost no agreed-upon recommendations for primary prevention of asthma (see page 21, lines 15 through 12 from the bottom).

2. The amount of direction or guidance provided and the presence or absence of working examples

The specification fails to disclose any data to support the fact that using this method could prevent respiratory. Applicant provides results for an *ex vivo* assay (example 7) that shows that BH4 was able to reduce superoxide production in lungs treated with a pro-inflammatory stimulus. This assay could be used as evidence for the possible use of this compounds in treating some respiratory diseases, but not for preventing these diseases.

3. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used for the prevention of respiratory diseases.

Only one compounds (see example 7) was tested *ex vivo* assays. Determining if any particular claimed compound would prevent a respiratory disease would require

synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by applicants.

Accordingly, the inventions of claims 1-7 and 11-15 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmid et. al. (Publication No. WO 01/56551).

Instant claims 1-2 recite a method for treating a respiratory disease comprising administering BH4 (tetrahydrobioprotein). For instant claims 1-2, Schmid et. al. teach: a method useful for preventing or reversing acute pulmonary vasoconstriction, such as may result from pneumonia, inflammation of the lung, as well as those cases of chronic

pulmonary vasoconstriction which have a reversible component, comprising the use of BH4 (see page 12 last paragraph and page 13, first paragraph).

Instant claim 10 recites a commercial product comprising a pharmaceutical preparation of BH4 or a derivative thereof. For instant claim 10, Schmid et. al. teach: a pharmaceutical composition comprising BH4 (see claims 1-5).

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Takafumi et. al. al. (Publication No. EP0908182, cited by the applicant).

Instant claim 10 recites a commercial product comprising a pharmaceutical preparation of BH4 or a derivative thereof. For instant claim 10, Takafumi et. al. teach: a pharmaceutical composition comprising BH4 or a derivative thereof (see claim 1).

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Schmid et. al (Publication No. WO 01/56551), or Takafumi et. al. (Publication No. EP0908182, cited by the applicant), or Zimmerman et. al. (Publication No. WO 96/02245).

Instant claim 23 recites a trade package comprising as pharmaceutical agent BH4 or a derivative thereof and/or arginine or a derivative thereof. For instant claim 23, Schmid et. al. teach: a pharmaceutical composition comprising BH4 (see claims 1-5). For instant claim 23, Takafumi et. al. teach: a pharmaceutical composition comprising BH4 or a derivative thereof (see claim 1). For instant claim 23, Zimmerman et. al. teaches a medicament comprising L-NMMA (NG-monomethyl-L-arginine, an arginine derivative) (see claims 1-5).

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 10, 16-18 and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by Rabelnik et. al. (US Patent No. 6,544,994).

Instant claims 10, 16-18 and 23 recite a commercial product or a preparation or a pharmaceutical composition or a trade package, comprising BH4 or a derivative thereof (claim 10), or BH4 or a derivative thereof and arginine or a derivative thereof (claims 16-18) or BH4 or a derivative thereof and/or arginine or a derivative thereof (Claim 23). For instant claims 10, 16-18 and 23, Rabelnik et. al. teach: a pharmaceutical composition comprising at least: BH4 and arginine (see claim 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabelnik et. al. (US Patent No. 6,544,994).

Claims 1-7 and 11-15 recite a method for preventing or treating a respiratory disease or more specifically COPD comprising administering either BH4 or a derivative thereof, or BH4 and a derivative thereof and arginine or a derivative thereof. For claims 1-7 and 11-15 Rabelnik et. al. teach a method of treating disorders associated with the levels of NO (Nitric oxide) comprising the administration of BH4 and L-arginine (see abstract). They do not teach the specific treatment of respiratory diseases, however they do teach that: biological effects of nitric oxide are not limited to vascular relaxation, but are also important in the respiratory, urogenital and gastrointestinal system, etc (see column 2, lines 22-26).

Since the same art teaches that compounds or combination of compounds that influence the levels of NO can be used to treat respiratory diseases, and that particular combination could comprise BH4 and arginine; at the time of the invention was made, it would have been *prima facie* obvious for a person of ordinary skill in the art to treat any respiratory disease (including COPD) using a combination of BH4 and arginine, thus resulting in the practice of instant claims 1-7 and 11-15.

Claims 3-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmid et. al. (Publication No. WO 01/56551).

Claims 3-4 and 6 recite a method for preventing or treating COPD comprising administering BH4 or a derivative thereof. For claims 3-4 and 6 Schmid et. al. teach a method useful for preventing or reversing acute pulmonary vasoconstriction, such as may result from pneumonia, inflammation of the lung, as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, comprising the use of BH4 (see page 12 last paragraph and page 13, first paragraph). Although Schmid et. al do not specifically teach the treatment of COPD, since COPD is a respiratory disease associated with pulmonary vasoconstriction, at the time the invention was made, it would have been *prima facie* obvious for a person of ordinary skill in the art to treat COPD using BH4, thus resulting in the practice of instant claims 3-4 and 6.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcos L. Sznaidman whose telephone number is 571 270-3498. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 10/10/07

MLS
October 1, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

SDA